The Mechanism of Two Reactions leading to Isomeric 2-(*N,N*-Disubstituted Amino)thiazol-5-yl Ketones

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A study has been made of the condensations between *N*-acyl-*N'*,*N'*-disubstituted thioureas and α-halogeno ketones [reaction (**I**)], and between *N,N*-disubstituted thioureas and 2-bromo-1,3-diketones [reaction (**II**)]. The mechanistic details were elucidated by using substrates with pairs of (almost) equally reactive but spectrometrically distinguishable acyl groups, *e.g.*, CH_3CO and CD_3CO. In the presence of added base (triethylamine) both reactions proceed through a common open-chain 1,3-diketone; from this, isomeric products are formed by nucleophilic attack at the alternative carbonyl groups to give cyclic intermediates which then undergo rate-limiting dehydration. If base is not added the media become acidic. Reaction (**II**) follows its previous course but the relative rates of the stages are reversed. In reaction (**I**) the initial cyclic intermediate is dehydrated so rapidly that the open-chain 1,3-diketone is not formed, and only one isomer is produced.

Both reactions are useful preparatively. For example, by adding or omitting triethylamine a typical reaction (**I**) was induced to give 1-(5-*p*-methoxybenzoyl-4-*p*-nitrophenylthiazol-2-yl)hexahydroazepine (yield 79%) or the isomeric 4-*p*-methoxyphenyl-5-*p*-nitrophenyl compound (78%).

Some aspects of two routes to isomeric 2-(*N,N*-disubstituted amino)thiazol-5-yl ketones, set out as reactions (I) and (II) in Scheme 1, have been investigated previously;[1] only those features needed as background for the present work are repeated here. This report deals with the study of mechanistic features and, from an understanding of these, the development of a new and preparatively useful variation of reaction (**I**). To clarify presentation of the result Scheme 1 is organised as follows. The pairs of R^1 and R^2 groups used are denoted by the letters A—G, and the disubstituted amino groups by the symbol Ⓝ; the corresponding structures are shown beneath the reaction sequences. The product (**4**) from reaction (**I**) in which the 4-substituent (R^1) is derived from the *N*-acylthiourea (**2**) is termed the 'non-rearranged' product (NP), and that (**9**) in which the 4-substituent (R^2) comes from the α-halogeno ketone (**1**), the 'rearranged' product (RP). Although these terms cannot be applied to reaction (**II**) the results are presented in a way which facilitates comparison with those of reaction (**I**). For example, reaction (**I**)**Eb** in ethanol [involving PhCONHC(S)N(Me)Ph (**2b**; R^1 = Ph) and $MeCOCH_2Cl$ (**1**; R^2 = Me, Hal = Cl)] gives mainly the RP (**9**; R^1 = Ph, R^2 = Me). Since the major product of reaction (**II**)**Eb** is the same compound it is again formulated in this way rather than in the alternative (identical) manner (**4**; R^1 = Me, R^2 = Ph). The structures of new thiazol-5-yl ketones and the composition of mixtures were established as discussed earlier;[1] some of the NPs obtained here had been prepared by a different, unambiguous route.[1b]

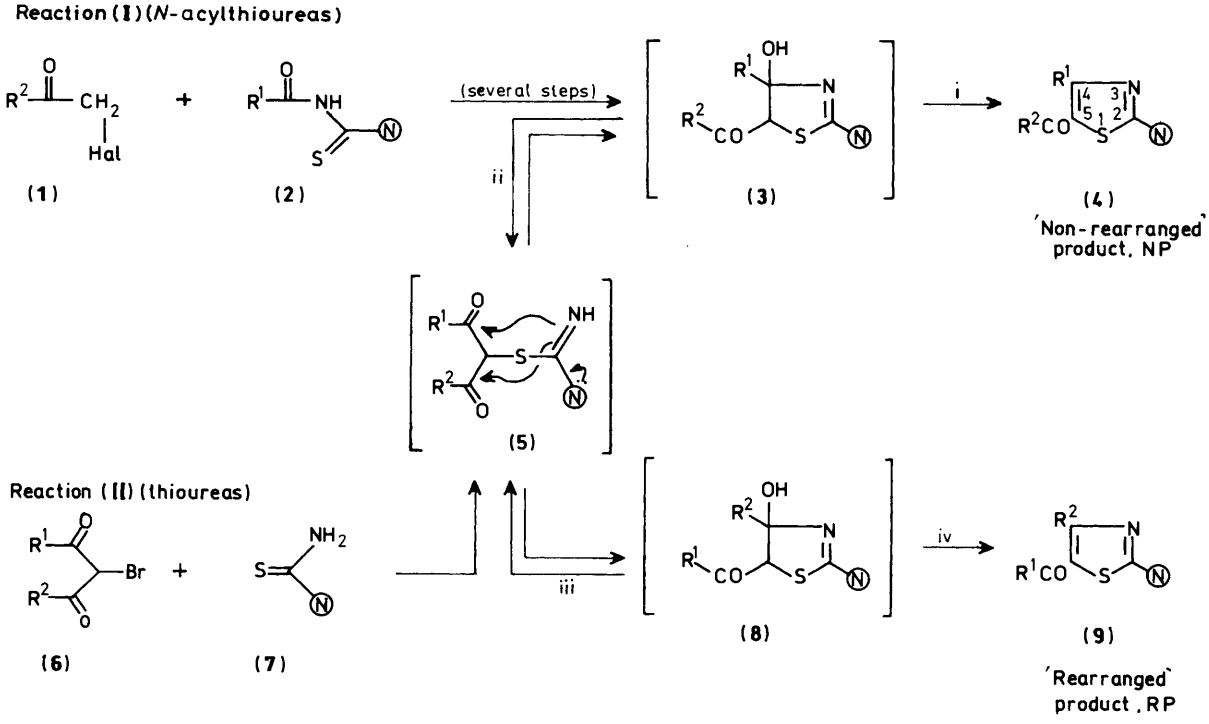
In general, reactions (**I**) and (**II**) give mixtures of NPs and RPs which arise from the involvement of the common intermediate (**5**) shown in Scheme 1. However for a pair of R^1, R^2 groups the RP:NP ratios of reaction (**I**) (as carried out previously using solutions in ethanol containing triethylamine) and reaction (**II**) (using solutions in acetone without added base) are not equal. In reaction (**II**) both cyclic intermediates (**3**) and (**8**) arise directly from the open-chain precursor (**5**), but in reaction (**I**) intermediate (**8**) is formed from, and hence later than, intermediate (**3**). If some of the first intermediate (**3**) in reaction (**I**) leaks to the NP(**4**), *i.e.*, there is competition between steps *i* and *ii*, this reaction will have the lower ratio. Surprisingly, for most of the pairs studied[1b] the lower ratios are associated with reactions (**II**).

To produce isomeric products the groups R^1 and R^2 must be different, but this requirement makes it difficult to obtain clear-cut information about the relative rates of the equilibrations (steps *i* and *ii*) and the dehydrations (steps *i* and *iv*). The present study is based on the use of pairs of (almost) equally reactive but spectrometrically distinguishable acyl groups, *viz.*, CH_3CO and CD_3CO, and PhCO and C_6D_5CO.[2] (Preparative work on the deuteriated substrates is discussed later.) Reaction (**II**) the simpler of the reactions, was studied first to validate some assumptions involved in this approach. Model experiments (**II**)**Ba**, (**II**)**Da**, and (**II**)**Db** (see Table) in which R^1 = R^2 (both phenyl or both methyl) were shown to give the normal products in high yield. In the corresponding experiments (**II**)**Aa**, (**II**)**Ca**, and (**II**)**Cb** with the R^1 and R^2 groups as protio-deuterio pairs the RP:NP ratios were found to be 1:1, as expected, irrespective of the absence or presence of triethylamine. Thus, complications which might arise from the incursion of secondary isotope effects are negligible at the level of accuracy of the present analyses (±3% for each component). Two important results emerged from the use of protio-deuterio pairs in reactions (**I**). Under the standard conditions, a medium of ethanol containing triethylamine,[1b] reactions (**I**)**Aa**, (**I**)**Ca**, and (**I**)**Cb** gave ratios of 1:1. (Although appreciable isotopic exchange occurred in the NPs formed from the acetyl-trideuterioacetyl substrates detailed examination of the total products removed any doubt about the correctness of the basic RP:NP ratios.) Under different conditions, solutions in acetone without base, the NPs were formed efficiently as the sole products in reactions (**I**)**Aa** and (**I**)**Ca**. [The third reaction, (**I**)**Cb**, was unsuccessful, as was the corresponding reaction (**I**)**Eb** listed lower down the Table. During an investigation [1b] into the influence of the *N*-acylthiourea's disubstituted amino group on the course of reaction (**I**) the *N*-methyl-*N*-phenylamino compounds were found to be considerably less reactive than, for example, the hexahydroazepin-1-yl compounds.]

The features of reaction (**I**) established so far are as follows: in ethanol containing 2 mol equiv. of base the equilibration between intermediates (**3**) and (**8**) *via* the open-chain form (**5**) (steps *ii* and *iii*) is much faster than the dehydration of either intermediates (steps *i* and *ii*), but in acetone without base the dehydration of intermediate (**3**) (step *i*) is much faster than its conversion into form (**5**) (step *ii*).

Typical substrates (system **E**, with R^1 = Ph and R^2 = Me)

Scheme 1. Reactions leading to isomeric 2-(*N*,*N*-disubstituted amino)thiazol-5-yl ketones



Of the halogeno ketones (**1**) all but $MeCOCH_2Cl$ and CD_3COCD_2Br have the structure R^2COCH_2Br

Ⓝ	R^1	R^2	R^1	R^2	R^1	R^2
a; Hexahydroazepin-1-yl	**A**; Ph	C_6D_5[a]	**E**; Ph	Me	**H**; C_6H_4OMe-*p*	Ph
b; N(Me)Ph	**B**; Ph	Ph	**F**; C_6H_4OMe-*p*	Me	**I**; C_6H_4OMe-*p*	$C_6H_4NO_2$-*p*
c; Morpholin-4-yl	**C**; Me	CD_3	**G**; C_6H_4OMe-*p*	Bu^t	**J**; Bu^t	Me
	D; Me	Me				

[a] 95% C_6D_5 + 5% C_6D_4H

were examined next. The ensuing results, together with those of the foregoing experiments, led to the interpretation summarised in Scheme 2. [This is concerned only with the steps involved in the formation of isomers; the preceding steps, formation of intermediates (**3**) and (**5**) in reactions (**I**) and (**II**) respectively, briefly discussed earlier[1a] are not included. Thus, reactions shown as rate-controlling in Scheme 2 may not necessarily be so for the complete sequences.] An important consideration is that in neutral media reactions (**I**) and (**II**) produce thiazol-5-yl ketones plus 1 mol equiv. of hydrogen halide; the latter can then facilitate the dehydrations, acid-catalysis of which is strongly suggested by related work.[3] Under such conditions reactions (**I**) and (**II**) differ markedly. In reaction (**I**)**Ea**, without added base, the formation of the intermediate (**3**) is followed by its rapid transformation into the NP(**4**), the sole product. However, in reactions (**II**)**Ea** and (**II**)**Eb** under these conditions both products are formed, and the RP:NP ratios reflect the relative reactivities of the acyl groups in the open-chain forms (**5a**) and (**5b**) (R^1 = Ph, R^2 = Me). As expected, the acetyl groups are the more electrophilic, and the small difference between the ratios is reasonably attributed to the change in the disubstituted amino group of the acylthioureas (**2a**) and (**2b**) (R^1 = Ph). When solutions in acetone containing triethylamine are used corresponding reactions (**I**) and (**II**) give the same RP:NP ratios, the outcome of relatively rapid interconversions between the intermediates (**3**), (**5**), and (**8**), and rate-limiting dehydrations.

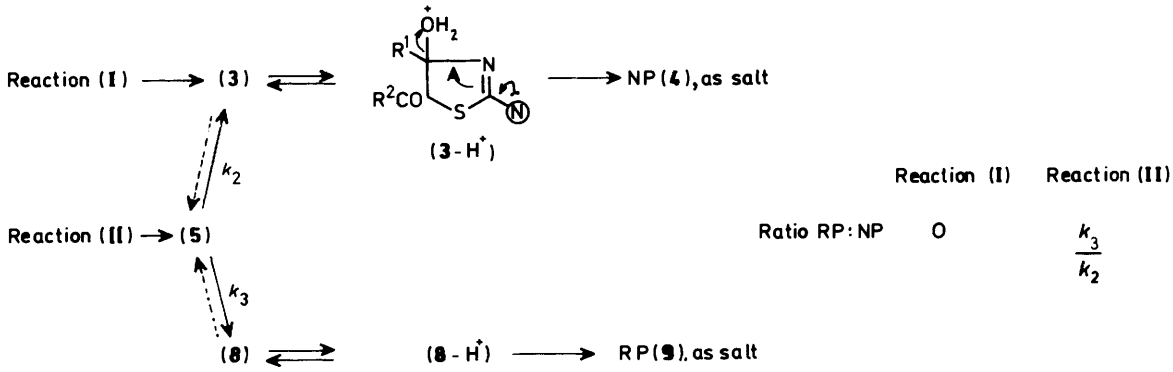
Certain facets remain obscure. One is the origin of the higher RP:NP ratios of reactions (**II**)**Ea** and **b** associated with the presence of triethylamine. It seems unlikely that the values of k_4 are appreciably bigger than those of k_1: indeed, it could be argued that the 4-phenyl intermediates (**3**; R^1 = Ph, R^2 = Me) should be dehydrated more readily than the 4-methyl isomers (**8**; R^1 = Ph, R^2 = Me). If the ratios k_4/k_1 are not much greater than unity the values of [(**8**)]/[(**3**)] must exceed those of k_3/k_2, and this implies unexpectedly large differences in stability between the intermediates [(**3**)] and [(**8**)]. A second uncertainty concerns the marked decreases in the ratios of reactions (**I**)**Jb** and **c** arising from the replacement of triethylamine by the stronger base DBU (last entries in the Table). It may be that the dehydrations are now base-catalysed, possibly as depicted in Scheme 2. The mechanistic situation would then revert some way to that of the neutral media, with the first-formed intermediates (**3Ja** and **b**) undergoing dehydration and isomerisation at comparable rates.

The third section of the Table illustrates the versatility of reaction (**I**) in preparative work. Reactions which under the standard conditions (ethanol containing triethylamine) lead mainly to the RPs (**9**) can be diverted to give the NPs by using acetone without base. Even when the outcome of the standard reaction is dominated by the much higher reactivity of one of the acyl groups, for example reaction (**I**)**Ia**, with a ratio of >20:1, the NP(**4**) is the sole product in the neutral medium.

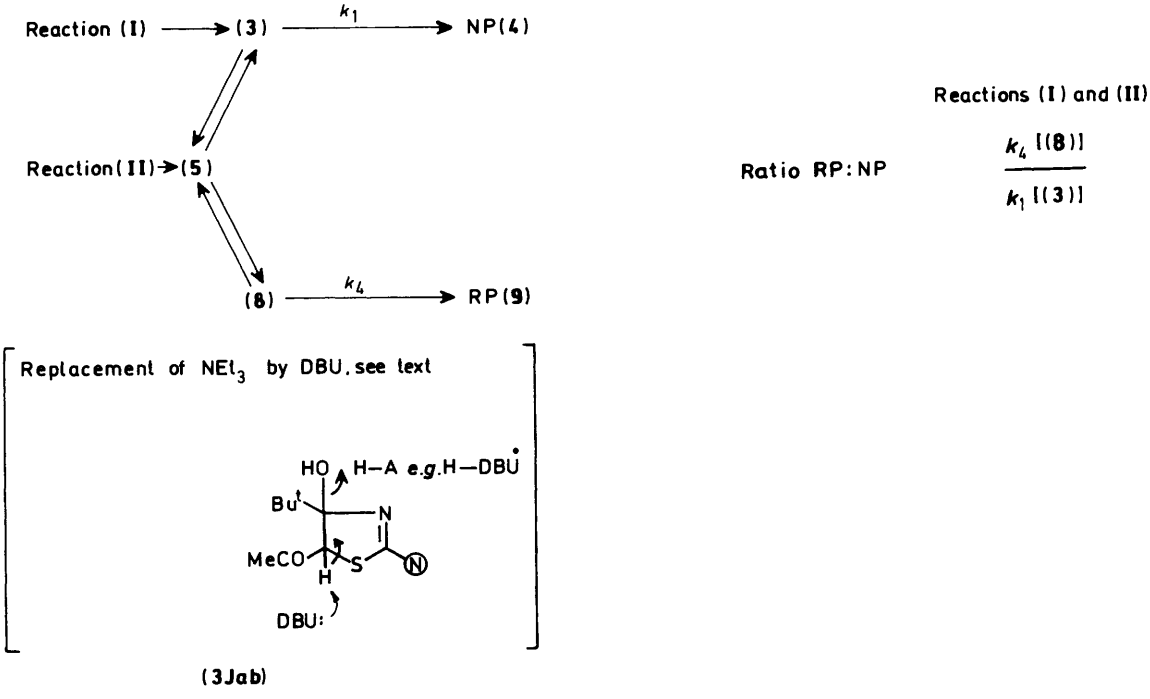
In the preparation of the aromatic deuteriated compounds

Scheme 2. Mechanisms of reactions leading to isomers

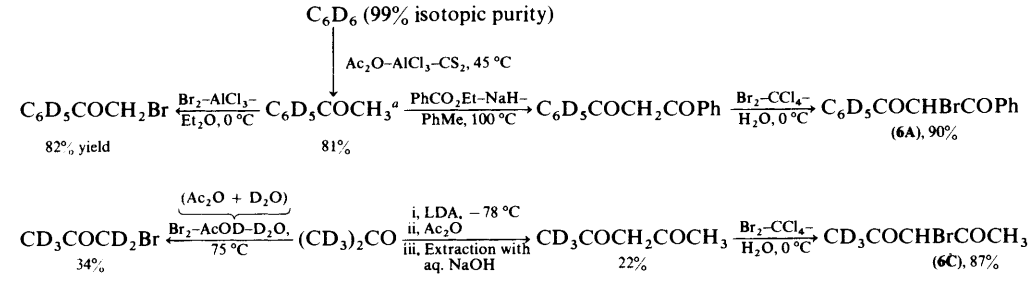
In neutral media. Formation of intermediates (**3**) and (**8**) rate-determining, dehydrations fast



In presence of NEt_3 (2 mol equiv.). Dehydrations rate-limiting, equilibration between (**3**) and (**8**) fast



Scheme 3. Preparation of deuteriated starting materials



[a] The aromatic ring of this compound and the products from it consisted of C_6D_5 (95%) and C_6D_4H (5%).

(Scheme 3) there was a small loss of isotope in the first stage, but the isotopic composition of the aromatic ring remained unaltered in the subsequent reactions. Bromo[$^2H_5$]acetone was prepared by a procedure which is more efficient (yield 34%) than the original method[4] (18%). In Claisen condensations of [$^2H_6$]acetone with ethyl acetate under conventional conditions (*e.g.* using sodium hydride) H/D scrambling in the pentane-2,4-dione so obtained destroyed the required distinction between

Table. Results of reactions (**I**) and (**II**)

The solutions were boiled under reflux for 6 h [reactions (**I**) in Me_2CO not containing base] or 2 h [other reactions (**I**)] or 30 min [reactions (**II**)]. Where the NP(**4**) is shown as the product isolated examination of the total product indicated the absence of the RP(**9**). In model experiments with $R^1 = R^2$ structures (**4**) and (**9**) are identical. Except where indicated the base is NEt_3. Relevant results from previous work[a,b] are included for comparison. References are given to known products; the rest are new.

Reaction	Solvent	Base (NEt_3) (mol equiv.)	Ratio RP:NP	Product(s) isolated	Reaction	Solvent	Base (NEt_3) (mol equiv.)	Ratio RP:NP	Product(s) isolated
Reactions with deuteriated substrates, and model experiments									
(I)Aa	EtOH	2	1:1	[**(4Aa)** + **(9Aa)**]	**(II)Ca**	Me_2CO	0, 1.05, and 2	1:1	[**(4Ca)** + **(9Ca)**]
(I)Aa	Me_2CO	0	0	**(4Aa)**	**(II)Da**	Me_2CO	0		**(4Da)**[=**(9Da)**][b]
(II)Aa	Me_2CO	0, 1.05, and 2	1:1	[**(4Aa)** + **(9Aa)**]	**(I)Cb**	EtOH	2	1:1	[**(4Cb)**[c] + **(9Cb)**]
(II)Ba	Me_2CO	0		**(4Ba)**[=**(9Ba)**]	**(I)Cb**	Me_2CO	0	*d*	
(I)Ca	EtOH	2	1:1	[**(4Ca)**[c] + **(9Ca)**]	**(II)Cb**	Me_2CO	0, 1.05, and 2	1:1	[**(4Cb)** + **(9Cb)**]
(I)Ca	Me_2CO	0	0	**(4Ca)**[c]	**(II)Db**	Me_2CO	0		**(4Db)**[=**(9Db)**][a]
Comparison of reactions (**I**) *and* (**II**) *with typical substrates*									
(I) Ea	EtOH	2	5:1	**(9Ea)**[b]	**(I)Eb**	EtOH	2	10:1	**(9Eb)**[b]
(I) Ea	Me_2CO	0	0	**(4Ea)**[b]	**(I)Eb**	Me_2CO	0	*d*	
(I) Ea	Me_2CO	1.05	10:1		**(I)Eb**	Me_2CO	1.05	15:1	
(I) Ea	Me_2CO	2	14:1		**(I)Eb**	Me_2CO	2	20:1	
(II) Ea	Me_2CO	0	2.5:1		**(II)Eb**	Me_2CO	0	3:1	**(9Eb)**, **(4Eb)**[b]
(II) Ea	Me_2CO	1.05	10:1		**(II)Eb**	Me_2CO	1.05	14:1	
(II) Ea	Me_2CO	2	13:1	**(9Ea)**[b]	**(II)Eb**	Me_2CO	2	21:1	
A range of reactions (**I**) *in* EtOH *plus base, and in* Me_2CO *without base*									
(I)Ec	EtOH	2	8:1	**(9Ec)**[b]	**(I)Ha**	Me_2CO	0	0	**(4Ha)**
(I)Ec	Me_2CO	0	0	**(4Ec)**[b]	**(I)Ia**	EtOH	2	>20:1	**(9Ia)**[b]
(I)Fa	EtOH	2	2.5:1	**(9Fa)**[b]	**(I)Ia**	Me_2CO	0	0	**(4Ia)**
(I)Fa	Me_2CO	0	0	**(4Fa)**	**(I)Jb**	EtOH	2	18:1	**(9Jb)**[b]
(I)Ga	EtOH	2	*d*		**(I)Jb**	EtOH	2 (DBU)[e]	3.5:1	
(I)Ga	Me_2CO	0	0	**(4Ga)**	**(I)Jc**	EtOH	2	3.5:1	**(9Jc)**, **(4Jc)**[b]
(I)Ha	EtOH	2	2:1	**(9Ha)**[b]	**(I)Jc**	EtOH	2 (DBU)[e]	1.5:1	

[a] J. M. Caldwell, G. D. Meakins, R. H. Jones, T. R. Kidd, and K. Prout, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2305. [b] Ref. 1b. [c] Exchange (D → H) occurred to an appreciable extent in the 5-CD_3CO group of the NP(**4**) but to only a negligible extent in the 4-CD_3 group of the RP(**9**).[d] Reaction incomplete; analysis of complex mixture of starting materials and products not reliable. [e] 1,5-Diazabicyclo[5.4.0]undec-5-ene.

the acyl groups. Isotopic homogeneity was preserved by the controlled approach shown in Scheme 3; complete exchange (D → H) at the central carbon during work-up gave a product consisting entirely of [1,1,1-$^2H_3$]pentane-2,4-dione.

Experimental

Petroleum refers to light petroleum (dried and distilled; b.p. 105—115 °C).

Aromatic Deuteriated Compounds.—Ac_2O (distilled; 27.2 g) was added during 40 min to a stirred suspension of $AlCl_3$ (80.3 g) in [$^2H_6$]benzene (99% purity; 17.7 g)–dry CS_2 (90 ml) at 10 °C. The mixture was stirred at 45 °C for 1 h, cooled, poured into 10M HCl (200 ml)–ice (100 g), and stirred vigorously until the Al salts dissolved. The oil obtained after separation of the layers and extraction of the aqueous layer with more CS_2 was distilled to give material (21.3 g), b.p. 78—79 °C/10 mmHg, δ_H 2.23 (3 H, s, Me). This was shown by m.s. examination [*m/z* 125 (27.50%), 124 (1.45), 110 (100), and 109 (5.3)] to consist of [2′,3′,4′,5′,6′-$^2H_5$]acetophenone (95%) and compound(s) (5%) with four deuterons in the aromatic ring.

Br_2 (12.5 g) was added during 20 min to a stirred suspension of $AlCl_3$ (0.85 g) in the foregoing product (8.1 g) and dry Et_2O (50 ml) at 0 °C. The mixture was stirred for 2 h, and then worked up to give material (10.8 g), b.p. 110—112 °C/3 mmHg, m.p. 47—49 °C, δ_H 4.51 (2 H, s, CH_2Br) shown by m.s. examination [*m/z* 110 (100%) and 109 (5.3)] to be 1-bromo-[2′,3′,4′,5′,6′-$^2H_5$]acetophenone (95% isotopic purity).

Ethyl benzoate (12.1 g) and [$^2H_5$]acetophenone (95% isotopic purity; 8.75 g) were mixed, and added to a suspension of NaH (50% dispersion in oil; 6.72 g) in dry PhMe (50 ml). The mixture was stirred vigorously (Hirshberg stirrer) at 100 °C for 2 h, cooled, and ice–water (100 g) was added. The mixture was stirred for 10 min, and then poured into warm water (500 ml). AcOEt (100 ml) was added, the mixture was acidified with 10M HCl, the layers were separated, and the aqueous layer was extracted with more AcOEt. The material isolated from the combined AcOEt phases gave 2-([$^2H_5$]benzoyl)acetophenone (95% isotopic purity; 12.4 g), m.p. 78—79 °C (from petroleum); δ_H($CDCl_3$, product almost entirely in enolic form) 8.02(m) and 7.52(m) (5 H, Ph), and 6.87 (1 H, s, =CH); *m/z* 229 (M^+, 100%), 152 (34.10), 151 (1.79), 147 (35), 110 (47), 109 (3), and 105 (48); $\nu_{max.}$ 1 603 cm^{-1}.

A solution of Br_2 (2.76 g) in CCl_4 (20 ml) was added during 20 min to a vigorously stirred suspension of 2-([$^2H_5$]benzoyl)-acetophenone (3.97 g) in CCl_4 (35 ml)–H_2O (35 ml) at 0 °C. The layers were separated, and the aqueous layer was extracted with CCl_4. The CCl_4 phases were combined, washed with brine, and dried ($MgSO_4$). Evaporation at 20 °C/12 mmHg gave 2-([$^2H_5$]benzoyl)-2-bromoacetophenone (**6A**) (4.81 g), m.p. 99—101 °C (from petroleum); δ_H($CDCl_3$, compound almost entirely in ketonic form) 8.01(m) and 7.54(m) (5 H, Ph) and 6.58 (1 H, s, CHBr).

Aliphatic Deuteriated Compounds.—A mixture of Ac_2O (purified by fractional distillation, b.p. 139—139.5 °C; 7.5 g) and D_2O (15 g) was stirred at 75 °C for 10 min, and then [$^2H_6$]acetone (8.1 g) was added. Br_2 (24.3 g) was added during 45 min from a dropping funnel which had been drawn out to a fine nozzle (internal diameter *ca.* 1 mm). The mixture was cooled, dry K_2CO_3 was added until pH 8 was reached, and the mixture was shaken with dry Et_2O (3 × 50 ml). The Et_2O solution was treated with dry $MgSO_4$ and filtered, and the

solvent was evaporated at atmospheric pressure through a fractionating column. Fractional distillation gave bromo-[$^2H_5$]acetone (6.2 g), b.p. 44—45 °C/16 mmHg (lit.,[3] 42—44 °C/15 mmHg); *m/z* (chemical ionization) 156 and 154 [$(M + NH_4)^+$, 100%]; no ^1H n.m.r. signal.

A 1.5M solution of BuLi in hexane (97 ml) was added during 10 min to a stirred solution of Pr^i_2NH (15.1 g) in THF (200 ml) at 0 °C under N_2, and after 30 min the solution was cooled to −78 °C. [$^2H_6$]Acetone (8.95 g) was added during 5 min, and after a further 10 min Ac_2O (14.3 g) was added during 10 min. The mixture was stirred at −78 °C for 1 h after which the cooling bath was removed. After 2 h Et_2O (200 ml) and then 2M NaOH (75 ml) were added, the mixture was shaken vigorously, and the layers were separated. The organic layer was extracted with more 2M NaOH (2 × 20 ml), and the alkaline phases were combined, washed with Et_2O, acidified with 10M HCl, and extracted with Et_2O. The Et_2O solution was washed with water and then 1M $NaHCO_3$, dried, and evaporated at atmospheric pressure through a fractionating column. Distillation gave [1,1,1-$^2H_3$]*pentane-2,4-dione* (3.5 g), b.p. 128—130 °C/752 mmHg (Found: C, 58.1. $C_5{}^2H_3H_5O_2$ requires C, 58.2%); $\delta_H(CDCl_3)$ 15.4 (15% of total integral, broad s, enol OH), 5.52 (15%, s, enol =CH), 3.62 (10%, s, keto CH_2), 2.25 (15%, s, keto CH_3), and 2.06 (45%, s, enol CH_3); *m/z* 103 (M^+, 22%), 88 (20), 85 (21), 46 (98), and 43 (100).

Bromination of the foregoing diketone as described earlier gave 3-bromo[1,1,1-$^2H_3$]pentane-2,4-dione (**6C**) (87%); $\delta_H(CDCl_3)$ 15.82 (6% of total integral, broad s, enol OH), 4.74 (19%, s, keto CHBr), 2.61 (57%, s, keto CH_3), and 2.52 (18%, s, enol CH_3).

Reactions (**I**) *and* (**II**).—The reactions involving deuteriated substrates, and the model experiments (Table) are described. These are followed by the characterisations of new thiazol-5-yl ketones obtained in similar reactions. Analysis of total products (to establish RP:NP ratios, or the absence of RPs) was carried out by ^1H n.m.r. and/or m.s. examination; in some cases these methods did not give clear-cut results, and Fourier-transform i.r. analysis was then used. A complete account of the reactions and the analyses is recorded elsewhere.[5]

Reaction (**II**)**Ba**. A solution of 2-benzoyl-2-bromoacetophenone (**6B**) (3.05 g) in dry Me_2CO (20 ml) was added during 10 min to a stirred solution of 1-thiocarbamoylhexahydroazepine (**7a**)[1b] (1.58 g) in Me_2CO (20 ml). The solution was boiled under reflux for 30 min, cooled, poured into brine (100 ml), and basified with 18M NH_3. Extraction with AcOEt gave 4-(*5-benzoyl-4-phenylthiazol-2-yl*)*hexahydrozepine* (**4Ba**) (2.84 g), m.p. 116—117 °C (from petroleum) (Found: C, 73.0; H, 6.2; N, 7.8. $C_{22}H_{22}N_2OS$ requires C, 73.0; H, 6.1; N, 7.7%); δ_H 7.33 (5 H, m, PhCO) 7.07 (5 H, m, 4-Ph), and 3.70(m), 1.87(m), and 1.66 m (12 H, $[CH_2]_6$); $\nu_{max.}$ 1 611 cm^{-1}; *m/z* 362 (M^+, 100%) and 105 (39).

Reaction (**II**)**Aa**. 2-([$^2H_5$]Benzoyl)-2-bromoacetophenone (**6A**) (95% isotopic purity; 3.08 g) was used instead of compound (**6B**) in reaction (**II**)**Ba**. Work-up afforded material [3.10 g; *m/z* 110 (20%), 109 (1), and 105 (22)] which crystallised from petroleum to give a 1:1 mixture of products (**4Aa**) and (**9Aa**) (95% isotopic purity) (2.78 g), m.p. 115—116 °C; *m/z* 367 (M^+, 100%), 138 (5), 133 (5), 110 (29), 109 (1), and 105 (20).

The reaction was repeated twice, with NEt_3 (1.06 g) and then NEt_3 (2.02 g) present in the solution of 1-thiocarbamoylhexahydroazepine. Both gave a 1:1 mixture of products (**4Aa**) and (**9Aa**) (76% yield).

Reaction (**I**)**Aa**. A stirred solution of 1-(*N*-benzoylthiocarbamoyl)hexahydroazepine (**2a**; R^1 = Ph) (1.96 g) and $C_6D_5COCH_2Br$ (95% isotopic purity; 1.54 g) in dry Me_2CO (20 ml) was boiled under reflux for 6 h. Work-up gave material (1.56 g) which did not show a m.s. peak at *m/z* 105. Crystallisation from EtOH afforded 1-(5-[$^2H_5$]*benzoyl-4-phenylthiazol-2-yl*)*hexahydroazepine* (**4Aa**) (95% isotopic purity; 2.42 g), m.p. 115—116 °C (Found: C, 71.8. $C_{22}[^2H_5]H_{17}N_2OS$ requires C, 71.9%); *m/z* 367 (M^+, 100%), 110 (38), and 10 (2).

A stirred solution of the thiourea (**2a**; R^1 = Ph) (2.64 g), $C_6D_5COCH_2Br$ (2.06 g), and NEt_3 (2.04 g) in EtOH (20 ml) was boiled under reflux for 2 h. Work-up afforded material [3.61 g; *m/z* 110 (20%), 109 (1), and 105 (22)] which crystallised from EtOH to give a 1:1 mixture of products (**4Aa**) and (**9Aa**) (95% isotopic purity) (3.25 g), m.p. 114—115 °C; *m/z* 367 (M^+, 100%), 110 (20), 109 (1), and 105 (21).

Reaction (**II**)**Da**. 3-Bromopentane-2,4-dione (**6D**) (1.78 g) was used instead of compound (**6B**) in reaction (**II**)**Ba**. Work-up gave 1-(5-acetyl-4-methylthiazol-2-yl)hexahydroazepine (**4Da**)[1b] (1.81 g), m.p. 63—64 °C (from petroleum); δ_H 2.54 (3 H, s, 4-Me) and 2.40 (3 H, s, MeCO); *m/z* 238 (M^+, 100%) and 223 (53).

Reaction (**II**)**Ca**. 3-Bromo[1,1,1-$^2H_3$]pentane-2,4-dione (**6C**) (1.81 g) was used instead of compound (**6B**) in reaction (**II**)**Ba**. Work-up gave a 1:1 mixture of products (**4Ca**) and (**9Ca**) (1.79 g), m.p. 60—62 °C (from petroleum); δ_H 2.54 (1.5 H, s, 4-Me) and 2.40 (1.5 H, s, MeCO); *m/z* 241 (M^+, 100%), 226 (25), and 223 (24).

Reaction (**I**)**Ca**. A stirred solution of 1-(*N*-acetylthiocarbamoyl)hexahydroazepine (**2a**; R^1 = Ac) (420 mg) and bromo[$^2H_5$]acetone (336 mg) in dry Me_2CO (10 ml) was boiled under reflux for 6 h. Work-up gave material (415 mg) which did not show a m.s. peak at *m/z* 226. Purification by flash chromatography on SiO_2 with AcOEt–petroleum as eluant, and crystallisation from petroleum afforded material (324 mg) [m.p. 59—61 °C; δ_H 2.54 (2 H, s, 4-Me) and *ca.* 2.40 (several sharp signals, total integral 1.2 H, CHCO); *m/z* 241 (54%), 240 (79), 239 (58), 238 (17), and 223 (100)] with an average composition represented by structure (**4a**; $R^1 = CH_3$, $R^2 = CD_{1.8}H_{1.2}$).

A stirred solution of the thiourea (**2a**; R^1 = Ac) (425 mg), bromo[$^2H_5$]acetone (340 mg), and NEt_3 (428 mg) in EtOH was boiled under reflux for 2 h. Work-up followed by purification as in the foregoing experiment gave material (331 mg) [m.p. 60—62 °C; δ_H 2.54 (1.5 H, s, 4-Me) and *ca.* 2.40 (several signals, 2.06 H, CHCO); *m/z* 241 (100%), 240 (28), 239 (20), 238 (6), 226 (43), and 223 (44)] consisting of compound (**9Ca**) (50%) and a mixture represented by structure (**4a**; $R^1 = CH_3$, $R^2 = CD_{1.9}H_{1.1}$) (50%).

Reaction (**II**)**Cb**. A solution of the bromo diketone (**6C**) (1.42 g) in dry Me_2CO (15 ml) was added during 10 min to a stirred solution of the thiourea (**7b**) (1.29 g) in Me_2CO (25 ml), and the solution was boiled under reflux for 30 min. Work-up gave material (1.65 g); *m/z* 234 (38%) and 231 (38). Crystallisation from Pr^iOH afforded a 1:1 mixture of products (**4Cb**) and (**9Cb**) (1.52 g), m.p. 91—92 °C; δ_H 3.56 (3 H, s, NMe), 2.60 (1.5 H, d, 4-Me), and 2.36 (1.5 H, s, MeCO); *m/z* 249 (M^+, 100%), 234 (39), 231 (39), 206 (8), and 203 (8).

The 1:1 mixture was also obtained (yield 78%) when the foregoing experiment was carried out in the presence of NEt_3 (1.05 and 2 mol equiv.).

Reaction (**I**)**Cb**. A stirred solution of the thiourea (**2a**; R^1 = Ac) (1.04 g), bromo[$^2H_5$]acetone (0.77 g), and NEt_3 (1.01 g) in EtOH (20 ml) was boiled under reflux for 2 h. Work-up gave material (0.95 g), m.p. 90—92 °C (from Pr^iOH), consisting of compound (**9Cb**) (50%) and a mixture represented by structure (**4b**; $R^1 = CH_3$, $R^2 = CD_{1.8}H_{1.2}$) (50%).

Other New Thiazol-5-yl Ketones.—1-(5-p-*Methoxybenzoyl-4-methylthiazol-2-yl*)*hexahydroazepine* (**4Fa**) (yield 76%), m.p. 106—107 °C (from EtOH) (Found: C, 65.5; H, 6.6; N, 8.6. $C_{18}H_{22}N_2O_2S$ requires C, 65.4; H, 6.7; N, 8.5%); *m/z* 330 (M^+, 100%) and 135 (44); 1-(4-p-*methoxyphenyl-5-pivaloylthiazol-2-*

yl)hexahydroazepine (**4Ga**) (52%), m.p. 80—81 °C (Found: C, 67.5; H, 7.7; N, 7.5. $C_{21}H_{28}N_2O_2S$ requires C, 67.7; H, 7.6; N, 7.5%); δ_H 3.83 (3 H, s, MeO) and 1.31 (9 H, s, Bu^t); *m/z* 372 (M^+, 8%), 315 (100), and 163 (46); 1-(5-*benzoyl*-4-p-*methoxyphenyl*-*thiazol*-2-*yl*)*hexahydroazepine* (**4Ha**) (89%), m.p., 129—130 °C (from EtOH) (Found: C, 70.2; H, 6.1; N, 7.3. $C_{23}H_{24}N_2O_2S$ requires C, 70.4; H, 6.2; N, 7.1%); *m/z* 392 (M^+, 100%), 163 (26), 105 (46), and 77 (47); 1-(4-p-*methoxyphenyl*-5-p-*nitrobenzoyl*-*thiazol*-2-*yl*)*hexahydroazepine* (**4Ia**) (78%), m.p. 175—177 °C (from AcOEt) (Found: C, 63.2; H, 5.2; N, 9.5. $C_{23}H_{23}N_3O_4S$ requires C, 63.1; H, 5.3; N, 9.6%); *m/z* 437 (100%), 315 (8), 163 (36), and 150 (20).

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